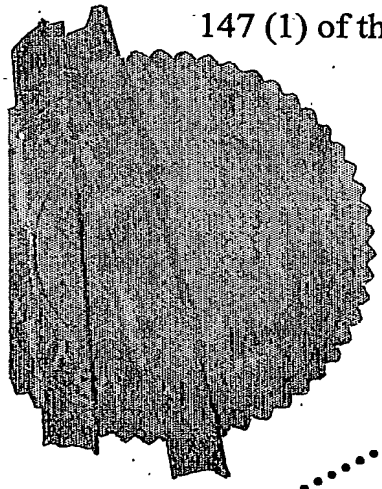
THE PATENTS ACT, 1970

IN/03/219

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application & Complete Specification filed on 20/06/2002 in respect of Patent Application No. 544/MUM/2002 of Sun Pharmaceutical Industries Ltd, Acme Plaza Andheri-Kurla Road, Andheri (E), Mumbai-400 059, Maharashtra, India. An Indian Company.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.



PRIORITY DOCUMENT
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Dated this 01 day of August 2003

M.A. Hafeez

(M.A. HAFEEZ)
ASST. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970
(39 OF 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

We, SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA

AN INDIAN COMPANY

hereby declare -

(i) that we are in possession of an invention titled "PROCESS FOR THE PREPARATION OF S-FLUOROMETHYL 6α, 9α-DIFLUORO-11β-HYDROXY-16α-METHYL-17α–PROPIONYLOXY -3-OXOANDROSTA-1,4-DIENE-17β–CARBOTHIOATE".

(ii) that the complete specification relating to this invention is filed with this application.

(iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are

1) Mr. Kambhampati Sudhakar 2) Dr. Chitturi Trinadha Rao 3) Dr.Thennati Rajamannar; of SUN PHARMA ADVANCED RESEARCH CENTRE, AKOTA ROAD, AKOTA, BARODA 390020, GUJARAT, INDIA; an Indian national.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

Dr. RATNESH SHRIVASTAVA,
INTELLECTUAL PROPERTY CELL,
SUN PHARMACEUTICAL INDUSTRIES LTD,
ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (E), MUMBAI-400 059, MAHARASHTRA, INDIA,
TELEPHONE NO-8397632, FACSIMILE NO- 8212110.

544/MUM/2002
20/6/2002

FORM 2

THE PATENTS ACT, 1970

(39 OF 1970)

COMPLETE SPECIFICATION

(See section 10)

PROCESS FOR THE PREPARATION OF S-FLUOROMETHYL 6α, 9α-DIFLUORO-11β-HYDROXY-16α-METHYL-17α–PROPIONYLOXY -3-OXOANDROSTA-1,4-DIENE-17β–CARBOTHIOATE

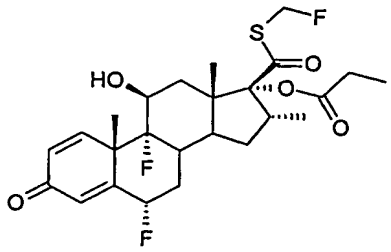
SUN PHARMACEUTICAL INDUSTRIES LTD.

A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed.

PROCESS FOR THE PREPARATION OF S-FLUOROMETHYL 6α, 9α-DIFLUORO-11β-HYDROXY-16α-METHYL-17α–PROPIONYLOXY-3-OXOANDROSTA-1,4-DIENE-17β–CARBOTHIOATE

The present invention relates to the process of preparing S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate, a compound of **formula 1**. S-fluoromethyl 6α,9 α-difluoro-11 β-hydroxy-16 α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate, commonly known as fluticasone propionate (INN), is used as an anti-inflammatory and antipruritic agent.



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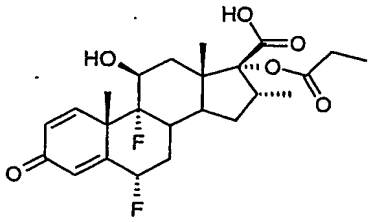
PRIOR ART

United States Patent No. **4335121 (referred to herein as the '121 patent)** discloses the compound of **formula 1** and its preparation. It discloses the process of its preparation by treating a compound of **formula 2** with dimethylthiocarbamoyl chloride to yield a compound of



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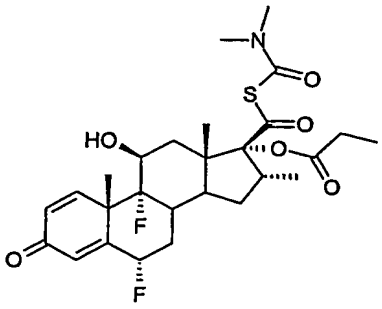

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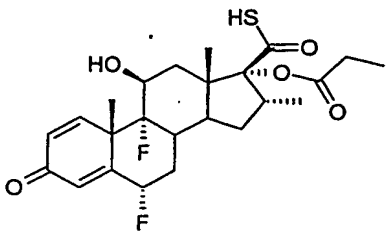

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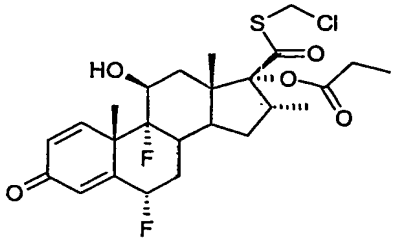

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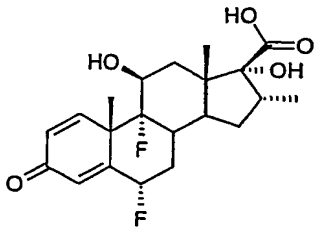
formula 3, which is decomposed by refluxing in diethylamine to the thioic acid of **formula 4**. An appropriate salt of the thioic acid of **formula 4** is then reacted with bromochloromethane to give a chloromethyl ester of **formula 5**. The compound of **formula 4,** is preferably converted to an iodomethyl ester by halogen exchange and subsequently treated with silver fluoride to yield the compound of **formula 1.** This process of preparation of the compound of **formula 1** is very tedious, lengthy, and involves use of expensive and sensitive chemical, viz. silver fluoride.

Gordon H. Phillipps et al,, **Journal of Medicinal Chemistry** 37, 3717-3729 (1994), disclose the method of preparing the compound of **formula 1** by treating a compound of **formula 6** with carbonyldiimidazole under nitrogen, followed by a reaction with hydrogen sulfide to give the thioic acid of **formula 7**, which is isolated and treated with propionyl chloride to give the compound of **formula 4.** This compound is then alkylated with bromofluoromethane under nitrogen to yield the compound of **formula 1** in only 69.3% yield. This reference does not mention the preparation of compound of **formula 1** directly from the compound of **formula 3.**



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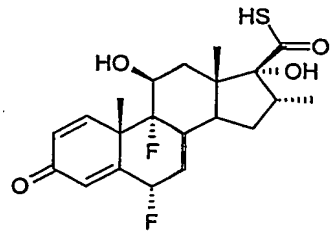

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PCT publication WO 01/62722 discloses the method of preparing the compound of **formula 1** by reacting a compound of **formula 2** with dimethylthiocarbamoyl chloride and molar equivalents of

sodium iodide in 2-butanaone to get compound of **formula 3**. The compound of **formula 3** is then reacted with sodium hydrosulfide to generate the sodium salt of **formula 4**, which is *in situ* alkylated with chlorofluoromethane to yield the compound of **formula 1.** This process albeit being simple has certain shortcomings viz. (i) the time taken for the completion of this reaction with chlorofluoromethane is very long, requiring about 26 hours. (ii) the amount of chlorofluoromethane required is in large molar excess, with almost 7.5 molar equivalents being used, and (iii) chlorofluoromethane being a gas would create handling difficulties. This invention does not disclose the preparation of compound of **formula 1** using bromofluoromethane, a liquid, which is easier to handle, as compared to the chlorofluoromethane gas.

OBJECT OF THE INVENTION

The object of the present invention is to provide a facile, efficient and economic process for the preparation of S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate.

SUMMARY OF INVENTION

We have found a facile, efficient and economic process for the preparation of S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate (compound of **formula 1**) that provides an improved yield of the compound, using reagents that are easy to handle, utilizing a low reaction time and using the reagents in lesser molar amounts.

The present invention provides a process for the preparation of S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate, a compound of **formula 1**, said process comprising,

(a) treating 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α–(propionyloxy)androsta-1,4-diene-17-β–carboxylic acid, a compound of **formula 2**, with N,N-dimethylthiocarbamoyl chloride in an inert aprotic solvent in the presence of a catalyst and a base to give a compound of **formula 3**;

(b) reacting the compound of **formula 3** with a hydrosulfide reagent and bromofluoromethane to yield a compound of **formula 1**; and

(c) optionally, purifying the compound of **formula 1**.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a two-step process for the preparation of compound of **formula 1** having a shorter reaction time and a high overall yield. Further, it uses bromofluoromethane, a liquid, which is easier to handle, as compared to chlorofluoromethane, a gas, which is used in the prior art process disclosed in the PCT publication **WO 01/62722**. The process of the present invention also utilizes lesser molar amounts of bromofluoromethane, as compared to the large molar amounts of chlorofluoromethane required in the prior art process. Also, the process of the present invention requires very low reaction times.

According to the process of the present invention, step (a) is carried out by treating the compound of **formula 1** with N,N-dimethylthiocarbamoyl chloride to give compound of **formula 2**. This may be done in the presence of a base and a catalyst. The base selected may be inorganic or organic. Examples of inorganic bases that may be used in the present invention include hydrides, hydroxides, carbonates, or fluorides of alkali or alkaline earth metals. The organic base may be selected from secondary or tertiary amines and quaternary ammonium bases which may be cyclic or acyclic, Preferably, the organic base is selected from hindered acyclic or cyclic tertiary amines and quaternary ammonium bases. In preferred embodiments, an organic base is used. More preferably, the organic base used is triethylamine.

The catalyst used in the process of the present invention may be an iodide salt selected from alkali metal iodides, alkaline earth metal iodides and quaternary ammonium iodides, the preferred catalyst being quaternary ammonium iodides, most preferably tetrabutylammonium iodide. The mole ratio of the catalyst to 6 α,9 α-difluoro-11β-hydroxy-16 α-methyl-3-oxo-17α–(propionyloxy)androsta-1,4-dien-17β–carboxylic acid that may be used in the process of the present invention lies in the range of about 0.01:1 to about 0.5:1, preferably 0.1:1.

The step (a) of the process of the present invention may be carried out in an inert aprotic solvent such as aliphatic or aromatic hydrocarbons, ethers, esters, nitriles and amides, or mixtures thereof. In preferred embodiments of the present invention ethers are used as the solvents. The ethers that are used are, cyclic or acyclic such as tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether,

tert-butyl methyl ether and the like, and mixtures thereof; more preferably tetrahydrofuran is used as the solvent.

The step (a) of the process of the present invention is carried out at temperature ranging from -10° C to 100° C, preferably from about 0° C to 25° C.
In a preferred embodiment of the process of the present invention, step (a) is carried out by treating the compound of **formula 1** with N,N-dimethylthiocarbamoyl chloride in tetrahydrofuran, in the presence of triethylamine and tetrabutyl ammonium iodide at room temperature, followed by cooling to 10 -15°C. The reaction mixture is warmed to ambient temperature and stirred for 2-8 hours, preferably for 4 hours. At the end of the reaction, the reaction mixture is treated sequentially with a polar aprotic solvent and water. The cation polar aprotic solvent may be selected from dimethylformamide, dimethylacetamide and dimethyl sulfoxide and the like; the preferred solvent being dimethylacetamide. The mixture is then cooled to 0° C, stirred and the compound of **formula 3** is filtered.

According to the process of the present invention, step (b) is carried out by reacting the compound of **formula 3** with a hydrosulfide reagent and bromofluoromethane.

In a preferred embodiment, the step (b) is carried out by reacting the compound of **formula 3** with a hydrosulfide reagent which may be selected from hydrated or anhydrous hydrosulfide salts, such as potassium hydrosulfide, sodium hydrosulfide, lithium hydrosulfulfide, quaternary ammonium hydrosulfides and the like. Preferably, sodium hydrosulfide is used in the process of the present invention. The hydrosulfide salt may be taken in a suitable solvent which facilitates nucleophilic substitution, such as dimethylformamide, dimethylacetamide, N-methylpyrrolin-2-one, dimethyl sulfoxide and the like; the preferred solvent being dimethylacetamide.

The mole ratio of bromofluoromethane to the compound of **formula 3** may be in the range of about 1:1 to about 5:1. Preferably, the mole ratio of bromofluoromethane to the compound of **formula 3**, used in the process of the present invention, is 3:1.

In a preferred embodiment of the process of the present invention, the compound of **formula 3** is treated with sodium hydrosulfide in dimethylacetamide at low temperature, like 0° C, for about one hour to about 6 hours, preferably for about 2 hours, followed by warming to room temperature and stirring for about one hour to about 5 hours, preferably for about 2 hours. The

mixture is then cooled to below 0° C, like –2° C to –10° C, preferably to about –5° C, and treated with bromofluoromethane. The reaction mixture is stirred further for about half an hour to about 4 hours, preferably for about 1 hour. At the end of the reaction, the mixture is preferably stirred with an oxidizing agent such as aqueous sodium hypochloride, sodium chlorite, hydrogen peroxide, and the like, preferably aqueous hydrogen peroxide, in order to oxidize other sulfide side products that may be formed during the reaction. The solid product is then filtered, washed with water and dried under vacuum to yield the compound of **formula 1**.

According to the process of the present invention, step (c) comprises purification of the compound of **formula 1** by treatment with a solvent system comprising one or more organic solvents. The ratio of the organic solvent to the compound of **formula 1** is in the range of about 1:1 to about 50:1. The organic solvents that may be used in the process of the present invention include alcohols, esters, ethers, ketones, amides, nitriles, aliphatic or aromatic hydrocarbons and mixtures thereof. Preferably the organic solvent used is an ester; more preferably the ester is ethyl acetate.

The starting material 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carboxylic acid, compound of **formula 2** used in this invention may be prepared in conventional manner e.g. by oxidation of 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3,20-dione-21-hydroxy- androsta-1,4-diene followed by reaction with propionyl chloride.

The present invention thus provides a facile and efficient process for the preparation of S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate (compound of **formula 1**). The process has the biggest advantage of improving the overall yield of the compound of **formula 1**. It has a low reaction times of about 6 hours, as compared to about 26 hours for step (b), required in the prior art processes (PCT publication **WO 01/62722**). The process utilizes bromofluoromethane, a low-boiling liquid that is easier to handle, as compared to chlorofluoromethane gas used in the prior art processes. Also, the amount of the chlorofluoromethane gas required for the preparation of the compound of **formula 1** in prior art (PCT publication **WO 01/62722**) is about 7.5 molar equivalents, whereas only about 3 molar equivalents of the bromofluoromethane are required in the present invention. The yield obtained in steps (b&c) in the present invention is 85%, compared to 70% reported for

the corresponding step in prior art (PCT publication **WO 01/62722**). These factors lead to increased economy of the process for this high value product of **formula I.**

The invention is illustrated but not restricted by the description in the following example.

EXAMPLE

Example 1

(a) **Preparation of 17β-[(N,N-dimethylcarbamoyl)thio]carbonyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-propionyloxy-3-oxoandrosta-1,4-diene :**

A solution of 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carboxylic acid, compound of **formula 2**, (50.0 g, 110 mmol) and N,N-dimethylthiocarbamoyl chloride (27.4 g, 222 mmol) in tetrahydrofuran (250 ml) at room temperature is cooled to 10 to 15° C. It is sequentially treated with triethylamine (24.9 g, 244 mmol) and tetrabutylammonium iodide (4.1 g, 11 mmol) at 10-15° C. The reaction mixture is warmed to room temperature, stirred for 4 hrs and then treated sequentially with dimethylacetamide (150 ml) and water (1.0 lit). The resultant mixture is cooled to 0° C, stirred for 2 hours, and the product is filtered. The solid obtained is washed with water (230 ml) and dried at 55° C for 4.0 hours to provide 57.0 g (96.0% yield, purity 98.5%) of compound of **formula 3**.

(b) **Preparation of S-fluoromethyl 6 α,9 α-difluoro-11β-hydroxy-16 α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate [compound of formula 1, fluticasone propionate]:**

A solution of 17β-[(N,N-dimethylcarbamoyl)thio]carbonyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-propionyloxy-3-oxoandrosta-1,4-diene, compound of **formula 3** (20.0 g, 37 mmol) and sodium hydrosulfide hydrate (9.4 g, 113 mmol) in dimethylacetamide (80 ml) at 0° C is stirred under nitrogen blanketing for 2 hours; warmed to room temperature and again stirred for 2 hours. The mixture is then cooled to –5° C, treated slowly with a solution of bromofluoromethane (12.6 g, 111 mmol) in dimethylacetamide (25 ml), and stirred for 1 hour. A 5% aqueous solution of hydrogen peroxide (40ml) was added and the mixture stirred for 0.5 hours at ambient temperature (reaction mixture should be positive to starch iodide paper). It is then treated with a solution of sodium bicarbonate (7.5 g) in water (375 ml) at –5° C, stirred for 1 hour, and filtered to provide a solid. The solid is washed with water (250 ml) and dried at 55° C under vacuum, to provide 20 g of crude compound of **formula 1** (purity >97%).

(c) **Purification of the crude S-fluoromethyl 6 α,9 α-difluoro-11β-hydroxy-16 α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate [compound of formula 1, fluticasone propionate]:**

The compound of **formula 1** (obtained as in example b) is dissolved in ethyl acetate (0.8lit.), stirred with 5% aqueous sodium carbonate solution (200 ml), and the mixture is filtered through Hyflo® bed. The aqueous layer is separated out and back extracted with ethyl acetate (200 ml). The combined organic extracts are sequentially washed with water (250 ml), 1.0N hydrochloric acid solution (200 ml), and water (200 ml). The organic layer is dried over anhydrous sodium sulfate, filtered through a micron filter (5 microns) and concentrated under reduced pressure at 40-45° C to ca. 60 ml. The suspension is refluxed for 30 min, gradually cooled to ambient temperature, stirred for 1 hour and the solid is collected by filtration. The solid obtained is washed with chilled ethyl acetate (30 ml, 10-15° C) and dried at 45° C under vacuum to provide 15.5 g (85%) of compound of **formula 1** meeting quality requirements as per British Pharmacopoeia.

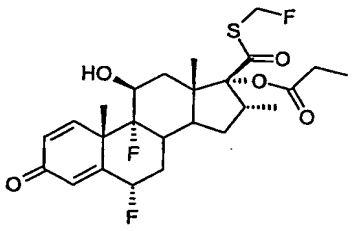
We claim:

1. A process for the preparation of S-fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate, a compound of **formula 1**, said process comprising -

   (a) treating 6 α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α–(propionyloxy)androsta-1,4-dien-17-β–carboxylic acid, a compound of **formula 2**, with N,N-dimethylthiocarbamoyl chloride in an inert aprotic solvent in the presence of a catalyst and a base to give a compound of **formula 3**;

   (b) reacting the compound of **formula 3** with a hydrosulfide reagent and bromofluoromethane to yield a compound of **formula 1**; and

   (c) optionally, purifying the compound of **formula 1**.



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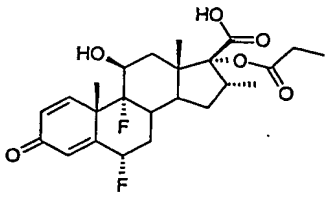

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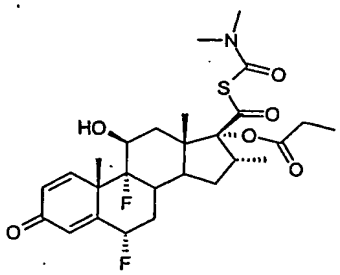

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2. A process as claimed in claim 1, wherein the inert aprotic solvent is an ether.
3. A process as claimed in claim 2, wherein the inert aprotic solvent is tetrahydrofuran.
4. A process as claimed in claim 1, wherein the catalyst is an iodide salt.
5. A process as claimed in claim 4, wherein the iodide salt.is tetrabutylammonium iodide.
6. A process as claimed in claim 1, wherein the mole ratio of the catalyst to 6 α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α–(propionyloxy)androsta-1,4-dien-17-β–carboxylic acid is 0.1:1.
7. A process as claimed in claim 1, wherein the base used is an organic base.
8. A process as claimed in claim 7, wherein the organic base is triethylamine.
9. A process as claimed in claim 1, wherein the hydrosulfide reagent used is sodium hydrosulfide.
10. A process as claimed in claim 1, wherein the mole ratio of bromofluoromethane to the compound of **formula 3** is 3:1.

11. A process as claimed in claim 1, wherein step (c) is carried out by treating the crude compound of **formula 1** with a solvent system.
12. A process as claimed in claim 11, wherein the solvent system comprises one or more organic solvent(s).
13. A process as claimed in claim 12, wherein the organic solvent is selected from alcohols, esters, ethers, ketones, amides, nitriles, aliphatic or aromatic hydrocarbons and mixtures thereof.
14. A process as claimed in claim 13, wherein the organic solvent is ethyl acetate.
15. A process as claimed in claims 1-15 substantially as herein described and illustrated by example 1.

Dated this 20th day of June, 2002.

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR,
SUN PHARMACEUTICAL INDUSTRIES LIMITED.

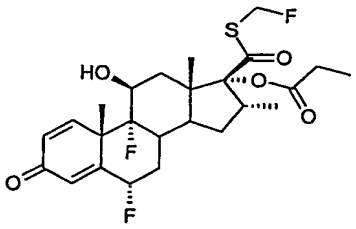
ABSTRACT

The present invention provides a process for the preparation of S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate, a compound of **formula 1**, said process comprising:

(a) treating 6α,9α-difluoro-11β-hydroxy-16 α-methyl-3-oxo-17α–(propionyloxy)androsta-1,4-diene-17-β–carboxylic acid, a compound of **formula 2**, with N,N-dimethylthiocarbamoyl chloride in an inert aprotic solvent in the presence of a catalyst and a base to give a compound of **formula 3**;

(b) reacting the compound of **formula 3** with a hydrosulfide reagent and bromofluoromethane to yield a compound of **formula 1**; and

(c) optionally, purifying the compound of **formula 1**.



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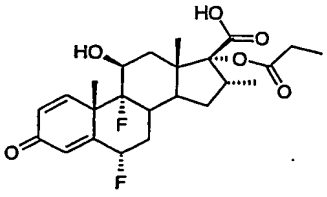

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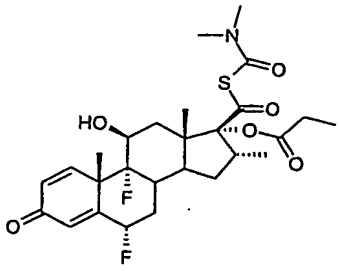

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